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Review Article

A REVIEW ON PLASMA THERAPY IN COVID-19 MANAGEMENT AND VITAL ROLE OF PLASMA DONATION

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Abstract

This article is focused mainly onconvalescent plasma therapy in COVID-19 management, its mechanism of neutralizing antibodies, steps of therapy along with the dosage, advantages, disadvantages and cautions. The extent and results of the investigational plasma therapy in India also has been mentioned. This article has a view on the importance, use, steps and vital role of plasma donation. Recently plasma therapy has been used as an investigational therapy in COVID-19 management due to lack of proper treatment or vaccine. Plasma is the liquid component of blood that transports cells, proteins, hormones, vitamins all over the body. Plasma helps support our immune system as it contains antibodies that defend foreign organisms. This is why plasma donations are so incredibly important. Several plasma banks have been set across the country. Plasma therapy is an immediate promising treatment option in the COVID-19 management. But however, it is only used for research and trial purposes until an ICMR study on it efficacy is completed.

Keywords: convalescent plasma, plasma therapy, passive immunity, COVID -19, SARS CoV-2, RNA virus, immunotherapy, neutralizing antibodies.

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INTRODUCTION

Plasma therapy or Plasmapheresis is the removal, treatment, and return or exchange of blood plasma or components thereof from and to the blood circulation. It is thus an extracorpeal therapy. Patients those are recovered from a disease have permanent antibodies generated by the immune system floating in their blood plasma, the liquid component of blood. To turn that into a drug, the plasma is to be harvested, test for safety, and purified to isolate those protective antibodies. When injected into a new patient, the plasma derived therapy also known as convalescent plasma therapy provides passive immunity until patients' immune system generates its own antibodies. This is classic adaptive immunotherapy, has been applied for to the prevention and treatment of many infectious diseases for more than one century [1]. Over the past two decades, the use of convalescent plasma (CP), the yellowish liquid obtained from the blood of a person recovering from illness was successfully used in the treatment of SPANISH FLU, SARS, MERS, and 2009 H1N1 pandemics. And now researchers are seeing an explosion of interest in using CP to treat COVID- 19

HISTORY OF CONVALESCENT PLASMA THERAPY:

This therapy is not a new concept this has been used since the 1800s. The first trail was done in 1892for treating diphtheria using blood serum initially. In 1920s, it was used to treat Scarlet fever, and later to treat pertussis until about 1970. During the Spanish flu influenza pandemic, 1918 CP was used as a potential therapy with mixed results. It has been used in variety of viral infections like measles, mumps, argentine hemorrhagicfever, parvovirus B19, Cytomegalovirus, MERS CoV, SARS, H1N1, H5N1, Ebola viruses [2].

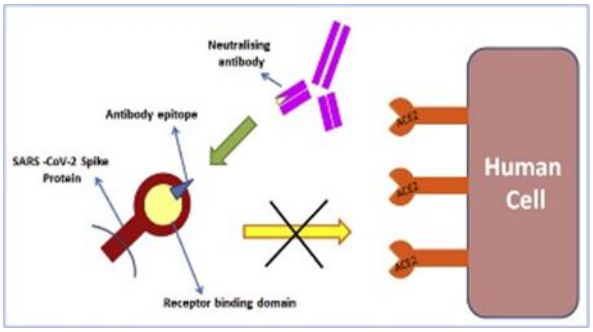
STRUCTURE OF SARS CoV-2:

The SARS-CoV-2 is an enveloped, single-stranded and positive (+) sense RNA virus. It belongs to the beta-CoV genera of Coronaviridae family. Structural proteins like membrane (M), nucleocapsid (N), spike protein (S) and envelope (E) protein play a vital role in the entry of virus and its replication in the host cell [3].

MECHANISM OF NEUTRLIZING ANTIBODIES FROM CONVALESCENT PLASMA:

The recovered patients of COVID-19 have high neutralizing antibody titre, which can be an important donor source of Convalescent Plasma

If nAbs specific to particular virus are administered in infected individual, it may reduce viral replication and disease severity. It may be possible means to limit the COVID-19 pandemic infection. The S protein of SARS-CoV-2 is one of the major targets for developing neutralizing antibodies to inhibit the binding and fusion of SARS-CoV-2. Neutralizing antibodies binds with Receptor Binding Domain (RBD) of the SARS-CoV-2 spike protein as shown in the aforesaid figure. The protruding portion (blue colour) highlights the antibody epitope 4.It has been reported that the ACE2 is the cell entry receptor for SARS-CoV-2 as like SARS-CoV because ACE2 shows binding to the receptor binding domain of both SARS-CoV and SARS-CoV-2 [5].



Schematic mechanism of neutralizing antibodies. Neutralizing antibodies binds with Receptor bonding domain (RBD) of the SARS-CoV-2 Spike protein and inhibits the binding of RBD to ACE2 receptor as shown in the figure. The protruding portion (blue colour) highlights the antibody epitope.

Effectiveness of CP therapy along with brincidofovir was also reported against the devastating Ebola virus disease in the year 2015 in Africa.6. The viral load decreased immediately after starting investigational therapy with CP in most of the infected persons.

CONVALESCENT PLASMA THERAPY IN COVID-19 MANAGEMENT:

Corona virus disease 19(COVID -19) is an emerging threat with major repercussions for public health. There are no approved specific antiviral agents targeting the novel virus, while some drugs are still under investigation. Currently, treatment of this disease is challenging and lack of evidence with antiviral agents is the rule. In such conditions historical interventions have remerged as option for the control of disease. Convalescent Plasma Therapy (CPT) emerges as a first option of management for hospitalized patients with COVID - 19. Convelescent plasma (CP) obtained from recovered COVID -19 patients who had established humoral immunity against the virus, containing large quantity of neutralizing antibodies.

STEPS OF CONVALESCENT PLASMA THERAPY:

1.To identify the blood donors who have been recovered from SARS–CoV-2 viral infections.

2.Pre-donation screening should be carried out. The donor should be free from any signs of SARS-CoV-2 infection and two negative results should be obtained for SARS-CoV-2 by molecular testing of blood or nasopharyngeal swab testing.

3.The informed consent of the donors should be collected.

4.The donor's blood grouping and screening for transfusion transmissible infections should be carried out.

5.The blood is to be withdrawn from the recovered person of COVID-19 infection, as per the standard parameters/established protocol.

6.The plasma has to be separated from whole blood and investigated for presence of virus-neutralizing antibodies by the experts.

7.The storage and transportation of CP to the respective hospitals for the transfusions.

8. Compatibility testing of critically ill and aged patients of COVID- 19 should be carried out.
9.The informed consent from a patient or his legal heirs (if unconscious) should be taken.
10.The respiratory rate of the patient should be > 24/min and SaO2 < 93% on room air or PaO2/FiO2 <300.
11.The clinical transfusion process should be carried out as per the existing protocol.
12.The continuous assessment of the success of this empirical therapy should be carried out for 7–10 days. The viral load, antibody levels and other clinical tests should be monitored.
13.The adverse effects (if any) after the administration of CP should be closely monitored.

CONVALESCENT PLASMA THERAPYDOSAGE :

The doses of CPT used as described by the different studies is varied. A Chinese pilot study showed a minimal use of a single dose of 200 mL convalescent plasma with neutralizing antibody titers >1:640. Another study by Bin Zhang et al8 reported a maximum of 2400 mL of convalescent plasma administered to a 73 years old male patient. Due to variability of CPT doses in reports, the optimal dose of CPT for COVID-19 could not be determined.

ADVANTAGES OFCONVALESCENT PLASMA THERAPY:

1. Passive immunization procedure that provides ready-made anti-COVID 19 antibodies.
2. Improvement of clinical symptoms like fever, cough, shortness of breath and chest pain within few days of CP transfusion.
3. Resolved from Acute Respiratory Distress syndrome (ARDS), weaned from ventilation within 1 day of administration of CP.
4. Reduction of pulmonary lesions on chest CT examinations.
5. Amelioration of routine laboratory criteria and pulmonary function.
6. Increase of neutralizing antibody titers.
7. Rapid reduction of viral load.
8. Enhances antiviral and anti-inflammatory properties.

DISADVANTAGES OFCONVALESCENT PLASMA THERAPY:

1. Cross contamination in case of poor handling.
2. May elicit a graft host reaction in the body due to blood transfers.
3. Adverse effects like allergic reactions, immune mediated tissue damage, transfusion associated circulatory overload, acute lung injury, hemolytic transfusion reactions.7

CAUTIONS OF CONVALESCENT PLASMA THERAPY

The risk of Hepatitis B virus, Hepatitis C Virus and HIV disease transmission through the donated plasma should be thoroughly investigated. Very limited information is available on the safety of CP therapy in pregnant patients of viral diseases; hence caution to be taken in pregnancy.

SCOPE OF PLASMA THERAPY TRAILS IN INDIA:

"Project PLACID" - Phase II Open Label Randomised Controlled Trail of convalescent plasma by ICMR has received the approval of COVID - 19 National Ethics Committee. Under this 21 hospitals across the country have been given permission to conduct stage II trails to assess the safety and efficacy of convalescent plasma therapy.

In Delhi, the first patient in India, who was treated with convalescent plasma therapy was recovered from COVID - 19 and was discharged. This patient admitted in the hospital with the history of respiratory problem and moderate symptoms. In the next two days his condition worsened and he developed pneumonia with type I respiratory failure. He did not respond to available therapy, therefore CP administration had started as per protocol from day 10 of infection. The progressive improvement was observed in patient from day 1 to day 4 of CP administration. The patient was successfully removed from infection within 10 days of transfusion of CP. Recently trails have been fastening up on patients with moderate to severe illness, and all have been positive outcomes.8

Three coronavirus patients were given convalescent plasma therapy at SMS hospital in Jaipur, it was reported that they showed improvement in clinical state, oxygen saturation and D-Dimer level.

In Mumbai, however Maharashtra's first novel patient to undergo the clinical trial for plasma therapy died. Another large patient enrollment in PLACID Trail was from RCSM Government medical college and CPR Hospital in Kolhapur, Maharashtra. Of 25 mild and moderate patients given plasma, 85% tested negative three days after the transfusion. The therapy on 5 severe patients who did not show any difference in outcome.

In Pune, the first experimental use of plasma therapy for treating a COVID 19 patient has been successful claimed by a senior doctor, Sassoon general hospital. The patient condition improved and tests on 14th day period came out negative. 9

In Punjab, first patient to be administered CP was discharged from hospital after he fully recovered from the disease at Guru Gobind Singh Medical College and Hospital GGSMCH. The Government Medical College and Hospital , GMCH, Amritsar has conducted Punjab's second and third successful CP therapy for coronavirus and patients recovered and discharged.

In Indore, Madhya Pradesh 4 COVID 19 patients recovered after plasma therapy at the privately run Sri Aurobindo Institute of Medical Sciences SAIMS.

In Gujarat, a patient who received plasma therapy was recovered and discharged from SVP Hospital.10

In Chennai, Tamil Nadu Rajiv Gandhi Government General Hospital (RGGGH) has led the way across the country by performing the highest number of plasma therapieson 26 persons so far, of these 24 patients have already been cured and discharged.

In Ganjam, Odisha 3 patients recovered after plasma therapy at TATA COVID 19 Hospital.

Of 5 patients COVID 19 effected patients who have been administered CP in Karnataka so far, 3 have recovered from disease and 2 succumbed to the disease.at Victoria hospital and Karnataka institute of medical sciences.

According to recent reports, another round of plasma therapy conducted on covid 19 patients at Noida, Uttar Pradesh was successful and all the 7 patients being discharged at GIMS.

In Telangana, plasma therapy on 5 coronavirus patients has shown positive results at Gandhi Hospital.

Recently the first COVID -19 patient who have undergone plasma therapy at Sri Venkateswara Institute of Medical Sciences, Vijayawada, Andhra Pradesh has recovered and discharged.

Many institutions which took part in the ICMR trail on plasma therapy have found to be effective for moderately ill patients. Out of 52 institutions participating in the ICMR PLACID trail, 24 institutions said plasma therapy was effective, 3 institutions doubt the effectiveness of plasma therapy.11

Even as multiple trails remain underway to establish its efficacy against disease that has battered the world, plasma banks have been setup to ease patients search for donors. As many cases recovered from COVID 19 in Delhi by plasma therapy, the Chief Minister appealed to all people who have recovered from the disease to come forward and donate plasma. Donating plasma would be an act of patriotism by recovered patients. It doesn't lead to any weakness in the body of donor. The people who have fully recovered from coronavirus would be saving lives of many people by donating their plasma. Many plasma banks have been setup across the country in various states. A patient who is willing to donate plasma may call 1031. Each plasma donation will be used to treat 2 patients.

PLASMA DONATION:

The liquid portion of the donor's blood is separated from the cells. Blood is drawn from one arm and sent through a high-tech machine that collects the plasma. The donor's red blood cells and platelets are then returned to the donor along with some saline [12].

IMPORTANCE OF DONATION:

- The plasma protein therapeutics industry supports volunteerism donation in all of its forms. Source plasma donation and blood donation are critically important activities that contribute to saving lives. 12
- Source plasma and recovered plasma are used as therapies to treat people with rare, chronic diseases and disorders such as primary immunodeficiency, hemophilia and a genetic lung disease, as well as in the treatment of trauma, burns and shock [12].
- Whole blood donations most often are used locally in hospitals for transfusions required during surgery or other medical treatment [12].

WHAT IS PLASMA USED FOR?

- Clotting Factors—People with bleeding disorders are unable to clot blood properly. As a result a minor injury may results in internal bleeding, organ damage and even death.
- Immunoglobulin or IVIG—More than 150 primary immune deficiency disorders (PID) are present. These individuals have improperly functioning immune systems and do not respond to traditional antibiotics. Without IVIG, they have been exposed to frequent and often serious infections.
- Alpha-1 Antitrypsin—Alpha-1 is commonly known as genetic emphysema. It is a heredity condition that may result in serious lung disease in adults and lung and/or liver disease in both children and adults.
- Albumin—Albumin is used to treat burns, trauma patients and surgical patients.
- Hyperimmuneglobulins—These are used to treat rabies, tetanus, dialysis patients and organ transplant recipients. They are also used to treat pregnant women who have Rh incompatibility, a condition where the mother and fetus have incompatible blood that can lead to serious injury to the unborn child or even death.

FINDING THE BEST CANDIDATE FOR CONVALESCENT PLASMA THERAPY:

Donor selection and timing of plasma extraction:

The U.S. Food and Drug Administration (FDA) has recommended the following guidance for timing of COVID-19 convalescent plasma collection:

- Scenario A (Clinical findings based): Donors' symptoms should have completely resolved at least 28 days before donation.
- Scenario B (Clinical plus laboratory investigation based): Donors' symptoms should have completely resolved at least 14 days before donation AND negative COVID-19 PCR from nasopharyngeal swab.

Convalescent plasma therapy involves many logistical challenges, including the donor's availability and willingness; apheresis center capacity; storage and transportation of plasma concentrate; and testing for the adequacy of antibody titers. Considering the aforementioned limitations and the potential risks, appropriate triage systems should be utilized; hence, plasma therapy use is currently restricted only to critically ill patients. The FDA recommends two clinical indications for the current usage of convalescent plasma therapy in **COVID-19 patients 13**

- Scenario A (Severe disease) which is defined as one or more of the following: Dyspnea, RR ≥30/min, blood oxygen saturation ≤93%, paO2/FIO2 Ratio <300, and radiological worsening with the appearance of lung infiltrates >50% within 24 to 48 hours.
- Scenario B (Life-threatening disease) which is defined as one or more of the following: Respiratory failure, septic shock, or multi-system dysfunction.

STEPS INVOLVED IN PLASMA DONATION:

1. Check-in: A friendly donation center team member will greet you and ask you to provide a valid photo ID, proof of your current address and your Social Security or

immigration card. Questions are asked of them to ascertain if they have participated in any high-risk behaviors or have any medical conditions that may disqualify them from donation

2. Physical Exam: To donate, individuals must meet certain requirements. They must be 18 years or older (19 years in Nebraska or 18 years with an authorized consent form), weigh at least 110 pounds and be in general good health. Donors must receive a physical evaluation during which their pulse, blood pressure and temperature are taken. He will also receive a confidential physical exam given by one of trained center medical specialists. He will receive a physical exam at least annually to make sure you remain in good health.14

3. Screening: Before the first donation, He will receive a health screening each time he donate to make sure he is in general good health and that you meet the donation criteria. They are also given a hematocrit test via a small finger prick to confirm a healthy level of red blood cells, and they must give a urine sample.14

4. Donation: New donors are required to donate two times. The second donation provides two sets of test results and health screenings to assure the safety and reliability of the plasma supply.If new donors donate only one time, their plasma donation is discarded. Plasma can be donated two times within a seven-day period with at least 24 hours between donations because the body replenishes the donated plasma within 24 to 48 hours.14

5. After Care: While plasma regenerates very quickly (usually within 24-48 hours) and plasmapheresis has few to no adverse effects, it is important to take care of their selfs after donation. Having something to eat and drink within two hours after donation helps replenish blood volume and restore your energy. 14

VITAL ROLE OF PLASMA DONATION:

Plasma is used to treat many rare genetic and chronic conditions caused by inability to produce plasma proteins in sufficient quantities. These individuals depend upon access to plasma therapies to treat bleeding disorders, immunological disorders, neurological disorders, and autoimmune diseases15.

Even in the present scenario, there is a compelling need to control the greatest global health crisis by COVID-19 outbreak. Convalescent Plasma Therapy is an immediate promising treatment option in the present COVID-19 pandemics.

But sustaining the need for these therapies requires large amounts of plasma that must be donated and then manufactured into lifesaving medicines. Hence, donation of plasma remains absolutely vital in the present scenario .Plasma Donation Needed from COVID -19 survivors. The patients who survived from COVID -19 and could help others do the same by donating their plasma. That plasma contains high levels of antibodies to SARS CoV- 2 that may be used to make an experimental treatment. This plasma could help to develop a treatment for COVID 19 and used for emergency purposes for critically ill COVID 19 patients. Even the world's leading plasma companies have formed the "COVID 19 Plasma Alliance" aimed at treating the new coronavirus with the collected plasma.In present pandemic more amount of plasma is needed to meet the therapeutic demand and save lives.

CONCLUSION: Convalescent plasma therapy is a safe and potentially effective strategy for the treatment of emerging and re-emerging pathogens, especially in those scenarios without proved antiviral agents or vaccines. Fingers crossed for a positive outcome for convalescent plasma use in COVID -19. We recognize that a definite conclusion cannot be drawn on treatment convalescent plasma therapy to COVID-19, a large multicenter clinical trials are urgently needed to tackle this pandemic. The FDA has recently allowed for the emergency use of COVID-19 as an "investigational therapy". Thus huge amount of plasma from completely recovered patients is necessary.With more plasma, manufacturers are expanding their fractionation production facilities and new technologies are being developed to meet therapeutic demand. The plasma donation business has ballooned into an enormous industry, and the demand allows plasma donors to be paid for their donation. Hopefully our article will be valuable for the pandemics.

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